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Prognostic Value of Myeloperoxidase in Patients with Chest Pain

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ABSTRACT

BACKGROUND

Inflammation is linked to adverse outcomes in acute coronary syndromes. Myeloperoxidase, an abundant leukocyte enzyme, is elevated in culprit lesions that have fissured or ruptured in patients with sudden death from cardiac causes. Numerous lines of evidence suggest mechanistic links between myeloperoxidase and both inflammation and cardiovascular disease.

METHODS

We assessed the value of plasma levels of myeloperoxidase as a predictor of the risk of cardiovascular events in 604 sequential patients presenting to the emergency department with chest pain.

RESULTS

Initial plasma myeloperoxidase levels predicted the risk of myocardial infarction, even in patients who are negative for troponin T (<0.1 ng per milliliter) at base line ($P<0.001$). Myeloperoxidase levels at presentation also predicted the risk of major adverse cardiac events (myocardial infarction, the need for revascularization, or death) within 30 days and 6 months after presentation ($P<0.001$). In patients without evidence of myocardial necrosis (defined as those who were negative for troponin T), the base-line myeloperoxidase levels independently predicted the risk of major adverse coronary events at 30 days (unadjusted 2nd, 3rd, and 4th quartile odds ratios, 2.2 [95 percent confidence interval, 1.1 to 4.6], 4.2 [95 percent confidence interval, 2.1 to 8.4], and 4.1 [95 percent confidence interval, 2.0 to 8.4], respectively) and at 6 months.

CONCLUSIONS

A single initial measurement of plasma myeloperoxidase independently predicts the early risk of myocardial infarction, as well as the risk of major adverse cardiac events in the ensuing 30-day and 6-month periods. Myeloperoxidase levels, in contrast to troponin T, creatine kinase MB isoform, and C-reactive protein levels, identified patients at risk for cardiac events in the absence of myocardial necrosis, highlighting its potential usefulness for risk stratification among patients who present with chest pain.

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Coronary thrombosis results in serious adverse cardiac events, even in the presence of aggressive intervention and treatment.[1-3] Levels of creatine kinase isoenzymes and cardiac troponins, which are diagnostic biologic markers of myocardial necrosis, are used either alone or in conjunction with levels of C-reactive protein as prognostic indicators of myocardial infarction.[4,5] Many patients with chest pain have normal levels of creatine kinase isoenzymes or troponins at presentation but subsequently have a myocardial infarction, require revascularization, or die within six months. Additional biochemical measures, ideally based on the pathophysiology of plaque vulnerability, are needed.

Inflammation has been linked to all stages of the development of vulnerable plaque, from initial lipid deposition to plaque rupture and its thrombotic complications. Evidence of leukocyte activation and degranulation is found in patients with unstable angina,[6-8] and extensive monocyte and neutrophil infiltration is seen in fissured, thrombosed plaques in patients with acute coronary syndromes.[9,10] In vitro studies suggest numerous mechanisms through which leukocytes may affect the stability of plaque in acute coronary syndromes. One potential participant is the leukocyte enzyme myeloperoxidase.

Myeloperoxidase levels are elevated in persons with angiographically documented cardiovascular disease[11] and within culprit lesions prone to rupture.[12] The activation of leukocytes prompts the secretion of myeloperoxidase and the generation of oxidants important in host defense.[13] Myeloperoxidase has been linked to the development of lipid-laden soft plaque,[14,15] the activation of protease cascades affecting the stability and thrombogenicity of plaque,[16,17] the production of cytotoxic and prothrombogenic oxidized lipids,[15,18] and the consumption of nitric oxide, leading to vasoconstriction.[19,20] In the study reported here, we tested the hypothesis that plasma levels of myeloperoxidase serve as a novel marker of plaque vulnerability in persons presenting to the emergency department with chest pain.

METHODS

STUDY DESIGN

Recruitment occurred as part of a study comparing troponin T levels with the levels of the MB isoform of creatine kinase (CK-MB) for the diagnosis of myocardial infarction.[21] Patients presenting to the emergency department within 24 hours after the onset of chest pain of suspected cardiac origin were eligible.

CLINICAL DIAGNOSIS

Myocardial infarction was defined by troponin T levels of at least 0.1 ng per milliliter. Unstable angina was ascertained on the basis of the presence of angina at rest, a sudden increase in episodes of previously stable angina, ST-segment depression, or T-wave inversions, as described previously.[21] Electrocardiographic data were verified independently by personnel at an electrocardiography core facility who were unaware of the patients' diagnoses. The diagnosis of an acute coronary syndrome was based on the presence of myocardial infarction or unstable angina, as defined in the protocol, and confirmed by a chart review by an investigator who was unaware of the patients' diagnoses.[21]

DEFINITIONS OF OUTCOMES

Patients were assessed for major adverse cardiac events (myocardial infarction, reinfarction, the need for revascularization, or death). A review of medical records and follow-up telephone interviews were conducted for the 30-day and 6-month outcomes. The need for revascularization was defined as coronary-artery bypass surgery, percutaneous coronary intervention, or catheterization in which at least two major coronary vessels were found to have stenosis of more than 70 percent.

DETERMINATION OF NORMAL MYELOPEROXIDASE LEVELS

For the determination of normal myeloperoxidase levels, sequential healthy subjects who responded to advertisements in a community newspaper were recruited between September and November 2002. Subjects who were at least 21 years old and who had no history or clinical evidence of coronary artery disease were eligible to participate. The control population had a mean (±SD) age of 49±12.4 years, 54.8 percent were men, 44.3 percent had a family history of coronary artery disease, 36.5 percent were current smokers, 2.6 percent had a history of diabetes, 2.2 percent had a history of hypertension, and 69.6 percent had a history of hyperlipidemia (low-density lipoprotein cholesterol ≥130 mg per deciliter [3.4 mmol per liter]).

All participants gave written informed consent. The institutional review board of the Cleveland Clinic Foundation approved the study protocol.

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loperoxidase levels were significantly elevated in those who had elevated cardiac troponin T levels (≥0.1 ng per milliliter) within the ensuing 4 to 16 hours, but not in those who were consistently negative for troponin T (median, 353 vs. 309 pM; P< 0.001).

The incidence of myocardial infarction increased with increasing quartiles of myeloperoxidase levels: it was 13.9 percent in quartile 1 (less than 119.4 pM), 16.6 percent in quartile 2 (119.4 to 197.9 pM), 25.2 percent in quartile 3 (198.0 to 393.9 pM), and 38.4 percent in quartile 4 (394.0 pM or more) (P<0.001 for trend). Patients who were initially negative for troponin T who subsequently had measurable levels at 4 to 16 hours were more likely to be in the third or fourth myeloperoxidase quartile than in the first or second quartile (proportion with ≥0.1 ng per milliliter troponin T levels, 5.3 percent of those in both quartile 1 and quartile 2, 8.0 percent of those in quartile 3, and 17.2 percent of those in quartile 4; P<0.001 for trend). Myeloperoxidase levels also correlated with the frequency of an adjudicated diagnosis of an acute coronary syndrome, increasing from 22.5 percent in quartile 1 to 58.0 percent in quartile 4 (P<0.001 for trend).

BASE-LINE LEVELS AND 30-DAY AND 6-MONTH OUTCOMES

Base-line myeloperoxidase levels were higher among patients who subsequently required revascularization or had a major adverse cardiac event (myocardial infarction, reinfarction, need for revascularization, or death) in the ensuing 30-day and 6-month periods than in those who did not have such complications (P<0.001 for all comparisons). Myeloperoxidase levels were also higher among the 34 patients who died within six months after presentation than among the 570 patients who did not die (median, 270 vs. 194 pM; P=0.05).

Myeloperoxidase levels were highest among patients who presented within 4.0 to 9.6 hours after the onset of symptoms (mean ±SE, 351±47 pM; P=0.041 for the comparison with patients who presented less than 2.0 hours after the onset of symptoms; P=0.002 for the comparison with those who presented more than 9.6 hours after the onset of symptoms). Myeloperoxidase levels remained a robust predictor of outcomes across the distribution of times between the onset of symptoms and the time of blood collection. Moreover, plasma myeloperoxidase levels in patients who presented less than two hours after the onset of symptoms (mean ±SE, 291±32 pM) were significantly higher than those in the control subjects (P<0.001).

MYELOPEROXIDASE LEVEL AS AN INDEPENDENT PREDICTOR OF RISK

The risk of myocardial infarction at presentation increased with increasing quartiles of base-line myeloperoxidase levels, both for the entire cohort and for patients with initially undetectable troponin T levels (P<0.001) (Table 2). Base-line myeloperoxidase levels also predicted the risk of major adverse cardiac events over the following 30-day and 6-month periods (P<0.001) (Table 2). The unadjusted odds ratios for major adverse cardiac outcomes within 30 days and 6 months for the highest quartile of plasma myeloperoxidase levels were 4.7 (95 percent confidence interval, 2.8 to 7.7; P<0.001) at 30 days and 4.7 (95 percent confidence interval, 2.9 to 7.7; P<0.001) at 6 months. Similar odds ratios and 95 percent confidence intervals were observed for plasma myeloperoxidase levels as a predictor of revascularization at both 30 days and 6 months (data not shown). Stratification based on sex revealed that although myeloperoxidase levels were lower in female patients than in male patients (P=0.05), these levels were similarly predictive of the risk of major adverse cardiac events at 30 days in both sexes (odds ratio for a major adverse cardiac event associated with a myeloperoxidase level in the fourth quartile, 8.3 [95 percent confidence interval, 3.4 to 20.2] for women and 3.5 [95 percent confidence interval, 1.9 to 6.5] for men).

To ascertain whether plasma myeloperoxidase levels independently predict the risk of revascularization, myocardial infarction, and major adverse coronary events, we used multivariate logistic-regression models. Adjustments were made for variables associated with myeloperoxidase levels or outcomes in univariate models (age; sex; C-reactive protein level; presence or absence of a history of hyperlipidemia, a history of revascularization, and a history of myocardial infarction; and electrocardiographic changes consistent with a diagnosis of an acute coronary syndrome). Adjusted odds ratios and 95 percent confidence intervals for the entire cohort were virtually identical to the unadjusted odds ratios, confirming that an elevated level of myeloperoxidase served as an independent predictor of increased risk of myocardial infarction, the need for revascularization, and major adverse coronary outcomes within 30 days and 6 months after presentation (P<0.001 for each comparison).

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BIOCHEMICAL ANALYSES

Troponin T levels were measured on an ES300 analyzer (Boehringer Mannheim). Base-line myeloperoxidase levels were measured with use of an enzyme-linked immunosorbent assay (Oxis). Each plate included a standard curve with isolated myeloperoxidase (extinction coefficient of 178,000 $M^{-1}cm^{-1}$)[22] and controls to correct for interplate variability. C-reactive protein levels were determined by high-sensitivity nephelometry (Dade Behring). CK-MB mass was measured by immunoassay (Abbott Laboratories).

STATISTICAL ANALYSIS

Continuous variables are presented as either means (±SD) or medians (with interquartile ranges), and categorical variables as numbers and percentages. Differences between groups in the outcome and associations among categorical variables were assessed with the use of the Wilcoxon rank-sum test. Trends for unadjusted analyses were evaluated with the use of the Cochran–Armitage trend test. Correlations among continuous variables were assessed with the use of the Spearman rank-correlation coefficient. Multivariate logistic-regression models (SAS version 8.0, SAS Institute) were developed to calculate odds ratios and 95 percent confidence intervals.

Table 1. Base-Line Characteristics of the 604 Patients.

Characteristic	Myocardial Infarction at Evaluation		P Value
	No (N=462)	Yes (N=142)	
Age — yr*	61.4±13.8	66.5±12.8	<0.001
Male sex — no./total no. (%)	254/462 (55.0)	100/142 (70.4)	0.001
History of coronary artery disease — no./total no. (%)	210/435 (48.3)	71/137 (51.8)	0.47
History of revascularization — no./total no. (%)	151/439 (34.4)	51/137 (37.2)	0.55
History of diabetes — no./total no. (%)	108/448 (24.1)	52/140 (37.1)	0.003
History of hypertension — no./total no. (%)	287/448 (64.1)	100/141 (70.9)	0.14
History of hyperlipidemia — no./total no. (%)	215/446 (48.2)	83/140 (59.3)	0.02
Current smoking — no./total no. (%)	92/439 (21.0)	42/137 (30.7)	0.09
History of smoking — no./total no. (%)	259/439 (59.0)	92/137 (67.2)	0.09

* Values are means ±SD.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The study population consisted of 604 sequential patients who presented to the emergency department with chest pain (Table 1). The mean time from the onset of chest pain to presentation was 4.0 hours. Final diagnoses included myocardial infarction in 23.5 percent, unstable angina in 17.1 percent, suspected coronary syndrome in 37.6 percent, and noncardiac chest pain in 21.5 percent. Outcomes at 30 days included myocardial infarction in 146 patients, death in 9 patients, revascularization in 189 patients, and a major adverse cardiac event in 245 patients.

MYELOPEROXIDASE LEVELS IN PATIENTS AND CONTROLS

Plasma levels of myeloperoxidase in patients presenting with chest pain ranged from 0 to 4666 pM, with a median of 198 pM and an interquartile range of 119 to 394 pM. These levels were significantly higher than those observed in the 115 control subjects (median, 120 pM; interquartile range, 97 to 146 pM; P<0.001). Myeloperoxidase levels in the patients were correlated weakly with peak troponin T levels (r=0.21, P<0.001), C-reactive protein levels (r=0.10, P=0.01), and age (r=0.11, P=0.01) but not the white-cell count (P=0.11). Median myeloperoxidase levels were higher in men than in women (213 vs. 184 pM, P=0.05). Median myeloperoxidase levels did not differ significantly according to smoking status or the presence or absence of a history of diabetes, hypertension, myocardial infarction, or coronary artery disease, but they were significantly higher in patients with a history of either hyperlipidemia (232 vs. 181 pM, P<0.01) or revascularization (234 vs. 189 pM, P<0.01).

BASE-LINE MYELOPEROXIDASE LEVELS AND RISK AT PRESENTATION

Myeloperoxidase levels were higher in patients who had a myocardial infarction within 16 hours after presentation than in those who did not (median, 320 vs. 178 pM; P<0.001). Among patients who had no biochemical evidence of clinically significant myocardial necrosis at presentation, base-line mye-

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loperoxidase levels were significantly elevated in those who had elevated cardiac troponin T levels (≥0.1 ng per milliliter) within the ensuing 4 to 16 hours, but not in those who were consistently negative for troponin T (median, 353 vs. 309 pM; P< 0.001).

The incidence of myocardial infarction increased with increasing quartiles of myeloperoxidase levels: it was 13.9 percent in quartile 1 (less than 119.4 pM), 16.6 percent in quartile 2 (119.4 to 197.9 pM), 25.2 percent in quartile 3 (198.0 to 393.9 pM), and 38.4 percent in quartile 4 (394.0 pM or more) (P<0.001 for trend). Patients who were initially negative for troponin T who subsequently had measurable levels at 4 to 16 hours were more likely to be in the third or fourth myeloperoxidase quartile than in the first or second quartile (proportion with ≥0.1 ng per milliliter troponin T levels, 5.3 percent of those in both quartile 1 and quartile 2, 8.0 percent of those in quartile 3, and 17.2 percent of those in quartile 4; P<0.001 for trend). Myeloperoxidase levels also correlated with the frequency of an adjudicated diagnosis of an acute coronary syndrome, increasing from 22.5 percent in quartile 1 to 58.0 percent in quartile 4 (P<0.001 for trend).

BASE-LINE LEVELS AND 30-DAY AND 6-MONTH OUTCOMES

Base-line myeloperoxidase levels were higher among patients who subsequently required revascularization or had a major adverse cardiac event (myocardial infarction, reinfarction, need for revascularization, or death) in the ensuing 30-day and 6-month periods than in those who did not have such complications (P<0.001 for all comparisons). Myeloperoxidase levels were also higher among the 34 patients who died within six months after presentation than among the 570 patients who did not die (median, 270 vs. 194 pM; P=0.05).

Myeloperoxidase levels were highest among patients who presented within 4.0 to 9.6 hours after the onset of symptoms (mean ±SE, 351±47 pM; P=0.041 for the comparison with patients who presented less than 2.0 hours after the onset of symptoms; P=0.002 for the comparison with those who presented more than 9.6 hours after the onset of symptoms). Myeloperoxidase levels remained a robust predictor of outcomes across the distribution of times between the onset of symptoms and the time of blood collection. Moreover, plasma myeloperoxidase levels in patients who presented less than two hours after the onset of symptoms (mean ±SE, 291±32 pM) were significantly higher than those in the control subjects (P<0.001).

MYELOPEROXIDASE LEVEL AS AN INDEPENDENT PREDICTOR OF RISK

The risk of myocardial infarction at presentation increased with increasing quartiles of base-line myeloperoxidase levels, both for the entire cohort and for patients with initially undetectable troponin T levels (P<0.001) (Table 2). Base-line myeloperoxidase levels also predicted the risk of major adverse cardiac events over the following 30-day and 6-month periods (P<0.001) (Table 2). The unadjusted odds ratios for major adverse cardiac outcomes within 30 days and 6 months for the highest quartile of plasma myeloperoxidase levels were 4.7 (95 percent confidence interval, 2.8 to 7.7; P<0.001) at 30 days and 4.7 (95 percent confidence interval, 2.9 to 7.7; P<0.001) at 6 months. Similar odds ratios and 95 percent confidence intervals were observed for plasma myeloperoxidase levels as a predictor of revascularization at both 30 days and 6 months (data not shown). Stratification based on sex revealed that although myeloperoxidase levels were lower in female patients than in male patients (P=0.05), these levels were similarly predictive of the risk of major adverse cardiac events at 30 days in both sexes (odds ratio for a major adverse cardiac event associated with a myeloperoxidase level in the fourth quartile, 8.3 [95 percent confidence interval, 3.4 to 20.2] for women and 3.5 [95 percent confidence interval, 1.9 to 6.5] for men).

To ascertain whether plasma myeloperoxidase levels independently predict the risk of revascularization, myocardial infarction, and major adverse coronary events, we used multivariate logistic-regression models. Adjustments were made for variables associated with myeloperoxidase levels or outcomes in univariate models (age; sex; C-reactive protein level; presence or absence of a history of hyperlipidemia, a history of revascularization, and a history of myocardial infarction; and electrocardiographic changes consistent with a diagnosis of an acute coronary syndrome). Adjusted odds ratios and 95 percent confidence intervals for the entire cohort were virtually identical to the unadjusted odds ratios, confirming that an elevated level of myeloperoxidase served as an independent predictor of increased risk of myocardial infarction, the need for revascularization, and major adverse coronary outcomes within 30 days and 6 months after presentation (P<0.001 for each comparison).

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Table 2. Odds Ratio for Major Adverse Cardiac Events According to the Quartile of Myeloperoxidase and C-Reactive Protein Level.*

Variable	Myeloperoxidase Quartile				C-Reactive Protein Quartile			
	1 (<119.4 pM)	2 (119.4–197.9 pM)	3 (198.0–393.9 pM)	4 (≥394.0 pM)	1 (≤1.925 mg/liter)	2 (1.926–5.470 mg/liter)	3 (5.471–11.640 mg/liter)	4 (>11.640 mg/liter)
	odds ratio (95 percent confidence interval)				*odds ratio (95 percent confidence interval)*			
Diagnosis at presentation								
Myocardial infarction								
All patients	1.0	1.2 (0.7–2.3)	2.1 (1.2–3.8)†	3.9 (2.2–6.8)‡§	1.0	1.9 (1.0–3.6)†	3.1 (1.7–5.8)‡	3.0 (1.6–5.4)†§
Patients initially negative for troponin T	1.0	1.0 (0.4–2.7)	1.5 (0.6–3.9)	3.7 (1.6–8.5)‡§	1.0	1.6 (0.7–3.6)	1.7 (0.8–3.9)	1.1 (0.5–2.7)
Adjudicated acute coronary syndromes								
All patients	1.0	1.6 (1.0–2.7)	3.5 (2.1–5.8)†	4.8 (2.9–7.8)†§	1.0	1.7 (1.1–2.8)†	2.0 (1.2–3.2)†	1.5 (0.9–2.3)
Patients persistently negative for troponin T	1.0	2.0 (1.0–4.2)	4.6 (2.3–9.2)†	4.1 (2.0–8.5)†§	1.0	1.5 (0.8–2.6)	1.2 (0.6–2.1)	0.6 (0.3–1.3)
Major adverse cardiac event								
At 30 days								
All patients	1.0	1.7 (1.02–2.8)†	3.2 (2.0–5.4)‡	4.7 (2.8–7.7)‡§	1.0	1.9 (1.2–3.1)†	1.7 (1.0–2.7)†	1.6 (1.0–2.5)
Patients persistently negative for troponin T	1.0	2.2 (1.1–4.6)†	4.2 (2.1–8.4)‡	4.1 (2.0–8.4)‡§	1.0	1.7 (1.0–3.0)	0.8 (0.4–1.6)	0.8 (0.4–1.5)
At 6 mo								
All patients	1.0	1.6 (1.0–2.7)	3.6 (2.2–5.8)‡	4.7 (2.9–7.7)‡§	1.0	1.8 (1.1–2.9)‡	1.7 (1.1–2.7)†	1.8 (1.1–2.8)†¶
Patients persistently negative for troponin T	1.0	1.9 (1.0–3.8)	4.4 (2.3–8.4)‡	3.9 (2.0–7.7)‡§	1.0	1.6 (0.9–2.7)	0.9 (0.5–1.7)	1.0 (0.6–1.9)

* In each analysis, the first quartile served as the reference group. Patients initially negative for troponin T had a troponin T level of less than 0.1 ng per milliliter at presentation.
† P<0.05 for the comparison with the first quartile.
‡ P<0.01 for the comparison with the first quartile.
§ P<0.001 for trend.
¶ P<0.05 for trend.

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CLINICAL OUTCOMES IN PATIENTS WHO WERE CONSISTENTLY NEGATIVE FOR TROPONIN T

To test whether myeloperoxidase levels serve not only as a marker of inflammation in response to myocardial necrosis, but also as a sensitive predictor of the presence of vulnerable plaques, we examined whether plasma myeloperoxidase levels predicted risk among patients presenting to the emergency department with chest pain but who have no evidence of myocardial necrosis (i.e., who are negative for troponin T throughout the monitoring period, from 0 to 16 hours after entry). Within this cohort of 462 patients, myeloperoxidase levels were significantly higher at base line in patients who had major adverse cardiac events in the subsequent 30 days and 6 months than in those who did not have such an event (median, 268 pM [interquartile range, 152 to 444] vs. 158 pM [interquartile range, 100 to 307]; $P<0.001$). Among patients who were negative for troponin T throughout the index presentation, the frequency of major adverse cardiac events at 30 days and 6 months increased with increasing base-line myeloperoxidase quartiles ($P<0.001$ for trend).

For patients who were consistently negative for troponin T, the risk of revascularization and other major adverse cardiac events at 30 days and 6 months increased with increasing quartiles of myeloperoxidase (Table 2). Figure 1 shows the unadjusted and adjusted odds ratios and 95 percent confidence intervals for myeloperoxidase quartiles as predictors of revascularization and major adverse cardiac events among these patients. Multivariate adjustment for factors associated with plasma myeloperoxidase levels and outcomes in the cohort had no significant effect on the risks, confirming that plasma levels of myeloperoxidase were strong and independent predictors of the 30-day and 6-month risks of revascularization and major adverse coronary events (Fig. 1).

COMPARISON WITH ESTABLISHED DIAGNOSTIC AND PROGNOSTIC BIOLOGIC MARKERS

To assess whether the predictive value of plasma myeloperoxidase levels is additive to that of C-reactive protein levels, parallel analyses were performed for C-reactive protein levels (Table 2). C-reactive protein levels predicted the risk of myocardial infarction at presentation for the entire cohort but were not predictive of major adverse cardiac events in the group that was negative for troponin T.

Receiver-operating-characteristic curves for the prediction of acute coronary syndromes and major

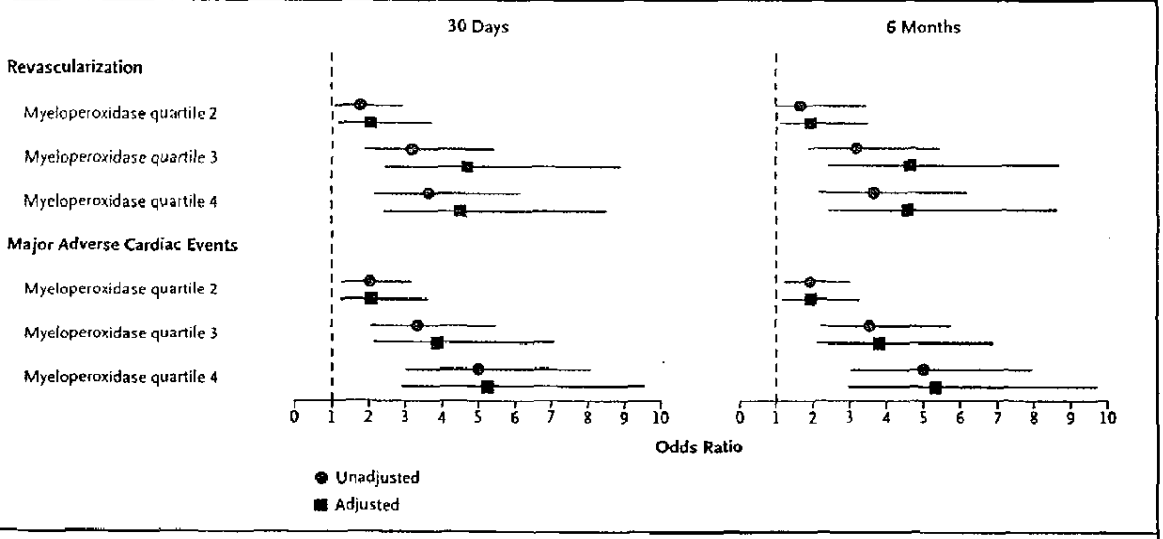

Figure 1. Risks of Revascularization and Major Adverse Cardiac Events among Patients Who Were Consistently Negative for Troponin T, According to Base-Line Myeloperoxidase Levels.

Odds ratios and 95 percent confidence intervals are shown. Adjusted odds ratios were adjusted for age; sex; C-reactive protein level; presence or absence of a history of hyperlipidemia, revascularization, or myocardial infarction; and electrocardiographic changes consistent with a diagnosis of acute coronary syndromes. For each comparison, the first quartile served as the reference group.

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adverse cardiac events were plotted for the entire cohort and for the cohort of patients who were consistently negative for troponin T (Fig. 2). In the cohort that was consistently negative for troponin T, the areas under the curve were highest for myeloperoxidase — significantly higher than those for troponin T (with the use of values of less than 0.1 ng per milliliter), CK-MB ($P<0.001$ for all comparisons for both outcomes), and C-reactive protein ($P<0.001$ for both outcomes). Using a cutoff point for myeloperoxidase (≥198 pM) that was derived from the receiver-operating-characteristic curve for the entire cohort (Fig. 2C), and established cutoff points for the other biologic markers,[23] we calculated the sensitivity, specificity, and positive and negative predictive values for troponin T (58.0 percent, 100.0 percent, 100.0 percent, and 77.7 percent, respectively), CK-MB (42.4 percent, 94.7 percent, 84.6 percent,

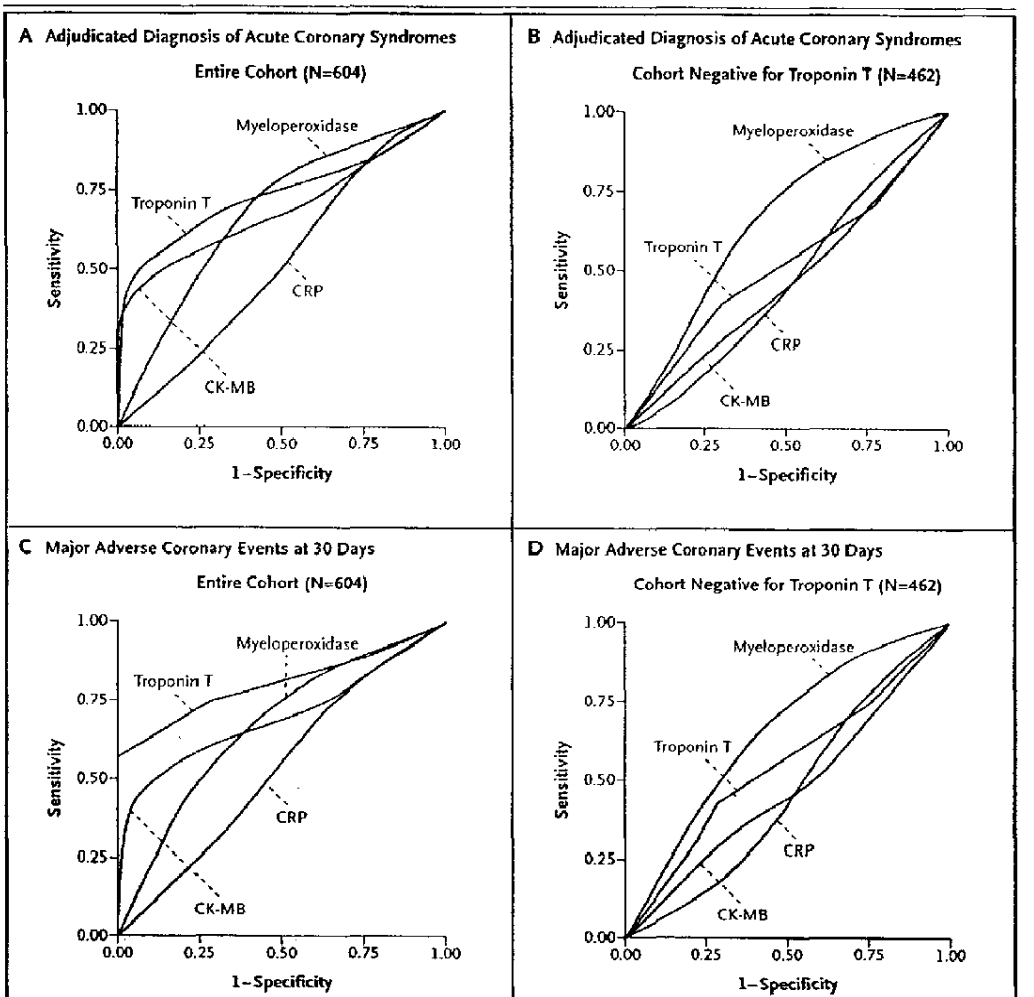

Figure 2. Receiver-Operating-Characteristic Curve Analyses of Biologic Markers for All 604 Patients (Panels A and C) and for the 462 Patients Who Were Consistently Negative for Troponin T (Panels B and D) for the Diagnosis of Acute Coronary Syndromes (Panels A and B) and Major Adverse Cardiac Events within 30 Days (Panels C and D).

Shown are receiver-operating-characteristic curves for the maximal values of troponin T and creatine kinase MB isoform (CK-MB) and base-line values of C-reactive protein (CRP) and myeloperoxidase. A negative result on the assay for troponin T was defined as a level of less than 0.1 ng per milliliter. The true positive fraction (sensitivity) is plotted against the false positive fraction (1 – sensitivity) to quantitate the diagnostic accuracy of each biologic marker.

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and 70.7 percent, respectively), C-reactive protein (31.7 percent, 68.9 percent, 40.6 percent, and 60.0 percent, respectively) and myeloperoxidase (65.7 percent, 60.7 percent, 53.3 percent, and 72.2 percent, respectively).

To evaluate the potential clinical value of base-line myeloperoxidase levels, we compared the positive test results with the negative test results for myeloperoxidase and other established biologic markers as a means of predicting unstable angina, myocardial infarction, acute coronary syndromes at presentation and major adverse cardiac events at 30 days (Table 3). Base-line measurement of myeloperoxidase levels significantly enhanced the identification of patients at risk despite being negative for troponin T, as compared with other markers (Table 3). The addition of myeloperoxidase to troponin T in the screening test significantly improved the ability to identify patients at risk for major adverse cardiac events at 30 days. With the use of troponin T alone, 58.0 percent of major adverse cardiac events were predicted, as compared with 84.5 percent with the addition of myeloperoxidase ($P<0.001$). Among patients who were consistently negative for troponin T, 22.3 percent still had a major adverse cardiac event in the ensuing 30-day period; however, with the addition of myeloperoxidase measurement to the screening test, this value was significantly reduced to 14.8 percent ($P<0.01$).

DISCUSSION

Clinical criteria, electrocardiographic criteria, and conventional laboratory tests do not adequately predict the risk of cardiovascular events in patients presenting with acute coronary syndromes. The use of C-reactive protein and other biologic markers has been advocated as a more accurate means of gauging risk, but additional tools that can predict the vulnerability of coronary arteries to major events in the near term are needed for patients who present with suspected acute coronary syndromes. Myeloperoxidase is an excellent candidate for the prediction of acute coronary syndromes because it is released by activated leukocytes, is elevated and catalytically active in vulnerable plaques, and has been mechanistically linked to factors affecting the development and stability of plaque.

Our results show that plasma myeloperoxidase levels predict cardiovascular risks independently of the levels of C-reactive protein and other markers of inflammation. An initial plasma myeloperoxidase level in patients who presented to the emergency department with chest pain provided information

Table 3. Comparison of Positive with Negative Test Results for the Measurement of Troponin T, Creatine Kinase MB, C-Reactive Protein, and Myeloperoxidase as a Means of Predicting Unstable Angina, Myocardial Infarction, and Acute Coronary Syndromes at Base Line and Major Adverse Cardiac Events (MACE) at 30 Days.*

Variable	Unstable Angina		Myocardial Infarction		Acute Coronary Syndromes		MACE at 30 Days in All Patients				MACE at 30 Days in Patients Negative for Troponin T	
	Ratio	χ^2	Ratio	χ^2	Ratio	χ^2	Ratio	χ^2	Value of Variable Alone	Additive Value of Variable plus Troponin T	Ratio	χ^2
									no. of positive results (%)			
Troponin T	0:103	38.0†	142:0	604.4†	142:103	270.2†	142:103	271.4†	142 (58.0)	—	0:0	—
Creatine kinase MB	5:98	18.0†	98:44	273.0†	103:142	120.3†	104:141	121.1†	104 (42.4)	148 (60.4)	6:97	0.03
C-reactive protein	24:79	3.5	55:82	5.6‡	79:161	0.3	76:164	0.007	76 (31.7)	163 (66.5)	21:82	4.3‡
Myeloperoxidase	67:36	11.5†	96:46	22.2†	163:82	45.0†	161:84	39.7†	161 (65.7)	207 (84.5)	65:38	18.1†§

* The ratios are the ratio of positive to negative test results. Cutoff points for the variables used were as follows: troponin T, ≥0.1 ng per milliliter; creatine kinase MB, ≥8.8 ng per milliliter; C-reactive protein, ≥10 mg per liter; and myeloperoxidase, ≥198 pM. A negative result on the assay for troponin T was defined as less than 0.1 ng per milliliter.

† $P<0.001$.

‡ $P<0.05$.

§ Myeloperoxidase levels predict the risk of major adverse cardiac events in the 30 days after presentation to the emergency department among patients consistently negative for troponin T. The addition of myeloperoxidase measurement to the measurement of troponin T as a risk-stratification strategy also significantly increased the overall sensitivity for the prediction of major adverse cardiac events.

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useful in determining the risk of myocardial infarction, revascularization, and major adverse cardiac events during the subsequent six months. Perhaps more important, even in patients in whom a myocardial infarction was ruled out on the basis of serial measurements of troponin T, an elevated myeloperoxidase level at presentation was predictive of subsequent major adverse cardiovascular outcomes.

Plasma myeloperoxidase levels correlated with troponin T levels and were predictive of acute myocardial infarction. However, whereas troponin T takes three to six hours to rise to measurable circulating levels after myocardial injury, myeloperoxidase levels were significantly elevated at base line (even within two hours after the onset of symptoms) in patients who were initially negative for troponin T. These findings suggest that measurement of myeloperoxidase levels may be useful in triage in the emergency department and that elevated plasma myeloperoxidase levels may be a marker of unstable angina preceding myocardial necrosis and therefore a predictor of vulnerable plaque.

Patients who present with chest pain but without evidence of myocardial necrosis are a diagnostically challenging group for risk stratification and one in which a means of identifying vulnerable plaque is needed. Perhaps the most interesting finding in the present study is that plasma levels of myeloperoxidase served as an excellent predictor of risk even in patients who were consistently negative for troponin T. In contrast, levels of C-reactive protein were not significantly predictive of risk in this group. C-reactive protein has been reported to serve as a predictor of the short-term risk of major adverse cardiac events in a subgroup of patients with acute coronary syndromes and undetectable levels of troponin T — those with persistent chest pain at rest.[24] However, a substantial proportion of patients who are negative for troponin T at presentation have more diagnostically challenging histories, and elevated levels of C-reactive protein are seen in less than 50 percent of patients in whom myocardial infarction is not preceded by unstable angina.[25]

Our findings suggest that myeloperoxidase serves as a marker of the vulnerable plaque and one that can be used to identify patients at imminent risk for major adverse cardiac events, independently of evidence of myocardial necrosis. Our results suggest that the addition of the measurement of myeloperoxidase to initial risk-stratification screening of patients presenting with chest pain may identify those at increased risk who might not otherwise be identified without invasive diagnostic testing. Further studies assessing free and leukocyte-associated myeloperoxidase levels as predictors of the short- and long-term risk of cardiovascular events, as well as the potential benefits of myeloperoxidase inhibition in patients with cardiovascular disease, are warranted.

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Dr. Hazen is named as a co-inventor on pending patents filed by the Cleveland Clinic Foundation that relate to the use of biologic markers of inflammation and cardiovascular disease.

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